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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/399,120
Filing Date: September 20, 1999
Appellant(s): MASCARENHAS, DESMOND

Desmond Mascarenhas
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 5-13-05.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: The rejection is maintained for claims 1-10, 16, and 18-48 under 35 U.S.C. §112, 1st paragraph, as not enabled by the specification.

(7) Grouping of Claims

The rejection of claims s 1-10, 16, 18-48 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Bayne et al. "The Role of Tyrosines 24, 31 and 60 in the High Affinity Binding of Insulin-Like Growth Factor-1 To the Type 1 Insulin-Like Growth Factor Receptor." Journal of Biological Chemistry, Vol. 265, No. 26, pp. 15648-15652. September 15, 1990.

Ngo et al. "Computational Complexity, Protein Structure Prediction, and the Levinthal Paradox." The Protein Folding Problem and Tertiary Structure Prediction. Ed. K. Merz and L. Le Grand. BirkHauser, Boston MA. pp. 491-495. 1994.

Rudinger, J. (1976). Peptide Hormones (ed. J.A. Parsons). University Park Press. Baltimore. pp. 1-7.

Jain, Rakesh. "Delivery of Molecular Medicine to Solid Tumors." Science, Vol. 271, pp. 1079-1080. February 1996.

Dermer, Gerald. "Another Anniversary for the War on Cancer." Bio/Technology, Vol. 12. March 1994.

Gura, Trisha. " Systems for Identifying New Drugs are Often Faulty." Science, Vol. 278, pp. 1041-1042. November 1997.

Golden, Fredrick. "Of Mice and Men: Don't Blame the Rodents" Time, pp. 44. May 18, 1998.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 16 and 18-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn the use of "null IGF-1" peptides in the treatment of cancerous tumors by inhibiting their growth

(2) The state of the prior art

The art indicates that native IGF-1 induces rather than inhibits tumor growth. The art has recognized that modified IGF-1 analogs, analogs that have replaced amino acids in positions 24, 31, or 60, have a loss of affinity for the 1 IGF receptor but retain affinity for type 2 IGF receptor. The

art, however, does not recognize that replacement of amino acids in IGF-1 receptor will result in an activity that inhibits the growth of cancerous tumors.

The state of the art with respect to animal models indicate that xenograft mouse models are poor predictors of tumor behavior in humans. Dermer states that "immunotherapy's killing power of the transformation of 3T3 cells by a mutated protooncogene, simply does not have the same significance for cells in vivo.' (See page 320). Further, "[t]he facts indicate, however, that petri dish cancer is really poor representation of malignancy, with characteristics profoundly different from human disease." (See page 320). Trisha Gura echoes similar sentiments in a *Science* article. The article indicates that the fundamental problem in cancer research is that model systems are not predictive of in-vivo activity (see page 1041). The article goes on to state xenograft models in mice "don't behave like naturally occurring tumors in humans--they don't spread to other tissues." (See page 1041). Further, other systems such as clonogenic assays are not always helpful since they "can't always predict how a tumor will respond to a drug in an animal" and "[s]ometimes they don't work because the cells simply fail to divide n culture." (See page 1042). In essence, the art indicates that "rodents are better predictors of human reaction to cardiovascular or anti-inflammatory agents than cancer or diseases of the central nervous system." (See *Time* article by Frederic Golden on page 44). Further, the Jain article states that for solid tumors, the clinical results to date have not met the high expectation obtained as a result of in in-vitro testing (see the paragraph of page 1079-1080). "Even with the best animal model, however, we still need to better understand how the process of biodistribution of various agents 'scales-up' from mouse to human. The biochemical and physiological differences between these species make this knowledge critical."

With respect to protein prediction, the art has recognized the difficulty in determining the three dimensional structure of a peptide solely based on structure. Ngo et al. teach that for proteins

and peptides, a " 'Direct' approach t structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task." (see page 493 in Ngo et al.) Accordingly, it is not known if an efficient algorithm for predicting the structure exist for a protein or peptide from it amino acid alone (see page 492 in Ngo et al.). Similarly, the Rudinger article (see the conclusions in particular) states "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study."

(3) The relative skill of those in the art

The relative skill of the those in the art is high.

(4) The predictability or unpredictability of the art

Applicants activity is based on the structure of the peptide. Since the activity is based on structure the predictability in the art is low. This due to the fact the art has recognized the difficulty in determining the three dimensional structure of a peptide solely based on structure. Ngo et al. teach that for proteins and peptides, a " 'Direct' approach t structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task." (see page 493 in Ngo et al.) Accordingly, it is not known if an efficient algorithm for predicting the structure exist for a protein or peptide from it amino acid alone (see page 492 in Ngo et al.). Similarly, the Rudinger article (see the conclusions in particular) states "The significance of particular amino acids or sequences for different aspects of biological

activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study."

(5) The breadth of the claims

The claims are drawn to a method of using "uncomplexed null insulin-like growth factor." The specification defines null IGF-1 as IGF-1 which has amino acid sequence alteration at one or more sites in the molecule (see page 5 of the specification). Further, Null-IGF-1 retains its activity in its ability to bind IGFBP-3, but is altered in its receptor binding and/or activating properties. The sequence of native IGF-1 contains 70 amino acids. Thus, the claims are drawn to the use of any IGF-1 analog wherein one of the amino acids have been altered in the in the native sequence for the slowing the growth rate of any tumor and for slowing the progression of cancer.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples

Although the specification provides guidance on how to make the peptides of the claimed invention, the specification has not provided ample guidance the effectiveness of peptides as inhibiting the growth rate of a tumor. As stated above, the specification implies that any sequence wherein the IGF-1 peptide has a differing amino acid from the native sequence will be effective in inhibiting the growth rate of a tumor. The working examples are limited to a single peptide, Y60L IGF-1, which was shown to be affective against prostate cancer. The specification does not disclose other modified peptides that are effective against tumor growth or disclose the effectiveness of peptide against different tumors. Although working examples are not necessary, it has been held that in unpredictable art, such as chemical cases more may be required. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving

chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result."

The specification has not provided guidance in the way of a disclosure of which any amino acids position, in the native IGF-1, that need to be maintained or should not altered in-order to obtained the desired activity. The activity is solely based on structures that have altered receptor binding activity. One cannot predict if a given modification in a peptide will have desired results in the inhibition of tumor growth. As stated previously, "'Direct' approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task. '(see page 492 in Ngo et al.) Accordingly, it is not know if an efficient algorithm for predicting the structure exist for a protein or peptide from it amino acid alone (see page 492 in Ngo et al.). Although the reference does not entirely rule out the algorithm, Ngo states that too many variables exist in obtaining an efficient algorithm. For example, the "Not knowing the computational complexity of side chain structure predication leaves the algorithm developer in the quandary of not known whether inexact methods are truly necessary..." (see page 495). Therefore, clearly one could not predict the three dimensional structure based on structure of peptide alone. Moreover, the true fact of the state of the art in peptide chemistry is expressed succinctly in the Rudinger article (see the conclusions in particular). "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study." It should be noted that reference of Bayne et al. (*J. Of Biol. Chemistry*, Vo. 265, No. 26) teach that replacement of Tyr 24 and/or Tyr 31 in IGF-1 affected the binding activity of

the peptide to the IGF-1 receptor. However, the reference further states that it could not be concluded "from our data whether the changes in affinity upon replacement of residues Tyr24 and/or Tyr31 are due to side chain or main chain interactions with the type 1 IGF receptor." (See page 15651). This implies, again, that one of ordinary skill cannot predict if the activity based on structure alone. As stated above, the specification has not provided any guidance as to what amino acids additions and/or amino acid changes should be avoided and/or desired. The only guidance provided in the specification is that the activity, with respect to the Type 1 receptor is, is altered such that there is "little or no binding" to the receptor. The specification does not set forth assay models whereby one could reasonably determine if the modification achieved the desired "little or no binding" to the type 1 IGF-1 receptor. It should be noted specification does not provide any guidance as what would constitute little binding affinity for the IGF-1 receptor. Thus one would be burdened with undue experimentation to determine which peptides, out of numerous possibilities, would be effective in achieving tumor growth suppression.

Finally, the claims are drawn to the treatment of all cancers. However, the specification has only shown effectiveness towards on single type of cancer. It is well known that the all cancers to not have the same mechanism of development and growth. Thus one could not assume that an agent effective against one tumor would be effective against all types of tumors. Moreover, animal models set forth for cancer are not good predictors of the efficacy in humans. As indicated in the state of the art with respect to cancer animal models, models in mice don't behave like naturally occurring tumors in humans--they don't spread to other tissues. In essence, the art indicates that "rodents are better predictors of human reaction to cardiovascular or anti-inflammatory agents than cancer or diseases of the central nervous system." (See Time article by Frederic Golden on page 44).

The cancer animal models and cell models, although provide valuable information for delivery of therapeutics, to not correlate to human in-vivo efficacy.

(8) The quantity of experimentation necessary

Since, the is uncertain to predict the helical structure of amino acid sequences based on structure alone, since contemporary hardware falls eight to nine orders of magnitude short of the task, and since different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the peptides would be effective in slowing the growth rate of tumors in a subject having cancer.

(11) Response to Argument

Appellants Arguments

The Ordinary Meaning of Null IGF is understood by a Skilled Artisan.

Appellants argue that references describing the state of the art regarding null IF at the time of filing were submitted with Appellant's April 7, 2003 response. These citations indicate that null IGF were defined at the time of filing of the instant application. "In addition, a person of skill in the art would know which amino acids could be changed based on these reference and the regions identified as 'critical' for the IGF receptor and IGFBP binding." Appellants assert that the specification describes precise modifications that can be made to an IGF molecule to render it "null," and discloses reference which illustrate null IGFs that are suitable for use in the claimed invention. Exemplary null IGFs are also outlined on page 5 and example 2 of the specification.

Claims Drawn to methods of Comprising Administering a Null IGF are Enabled

Appellants argue that Null IGF's were well defined at the time of filing and one of skill in the art would know how to make and use a null IGF in view of the literature and present specification. Moreover, Appellants presented a declaration that demonstrates that "null IGFs have a lower affinity for an IGF-I receptor but are still able to bind the major IGFBP-3 binding protein at least as well as wild-type IGF-I. Thus, it would be expected that any null IGF-I that satisfies these properties can be used to slow wild-type IGF-I induced tumor cell growth." The specification offers numerous null IGFs, including those where the tyrosine residue is replaced with non-aromatic residues, "variants where amino acid residues 49, 50, 51, 53, 55 and 56 are altered." Appellant's disclosure, in combination with knowledge known in the art at the time the application was filed, enables one skill in the art to practice the claimed invention.

Claims Drawn to Methods Comprising a Null IGF With a Substitution at Position 60 are Enabled

The working examples, in the specification, provide animal models for human prostate cancer using the null IGF Y60L. Results indicate that using this IGF variant, the mice treated "had a substantially greater survival." With respect to those claims drawn to null IGF-I where position 60 of the null IGF-I contains a non-aromatic residue substitution, one of skill in the art would expect that replacing the 60th amino acid would disrupt IGF receptor binding. The art indicates that position tyrosine 60 is pivotal for activity for IGF-I binding to type 1 IGF receptor. Thus alteration of this amino acid would affect IGF receptor binding and as such the claims are enabled.

Method of Treating Prostate Cancer are Enabled by the Specification

The working examples, in the specification, utilize human prostate PC-3 tumor xenografts. "While it is understood that no animal model is 100% predictive of the human condition, one cannot correctly conclude that efficacy of the therapeutic agent in an animal model bears zero correlation, with therapeutic efficacy in a person." None of the reference cited "indicate that there is no association between the pathogenesis of cancer in an animal model and a human." The enablement requirement does not require a per se rule that an animal model, used to support the claim of biological activity, be "art recognized." "Unless there is specific reason to doubt the correlation between a certain experimental animal and treatment of the disease condition itself, the evidence should be accepted presumptively." The art indicates that PC-3 animal model is frequently used by one of skill in the art to determine the therapeutic utility of a particular drug.

Methods for Treating Cancers other Than Prostate Cancers are Enabled by the Specification

Although the PC-3 animal model is a prostate cancer model, the therapeutic utility of Y60L in the PC-3 xenograft can be utilized to support the utility of a null IGF in other cancers. Indeed, the relationship between IGFs and cancer risk has been well studied and null IGFs are therefore suitable for slowing the growth rate and/or progression of any cancer for which IGFs have been implicated.

Response to Appellants Arguments

The specification does not define null IGF's as a specific subset of IGF. Rather, the specification defines null IGF as "IGF-I which has amino acid sequence alterations at one or more sites in the molecule." (see page 5, lines 16-25, emphasis added). The MPEP states "Where an explicit definition is provided by the applicant for a term, that definition will control interpretation

of the term as it is used in the claim. Toro Co. v. White Consolidated Industries Inc., 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999)." Here, using the definition of the specification, scope of the subset of IGF is enormous. IGF is a 70 amino acid molecule. Going by the definition in the specification, the possible variants are 70 to the 20 power or 7.979×10^{36} different variants. The specification demonstrates the activity of one variant against one cancer type.

Appallents state that "null IGFs" are well known in the art. However, the term "null IGF" is not well known in the art prior to Applicants filing of the instant application. A search on Chemical abstracts, the patent database, the international patent database, and other scientific journal database, for the term "null IGF" leads to five references. Three of these five references utilize Applicants definition. The other two identify the receptor rather than the "null IGF" molecule. Thus, in light of the art, the most concise meaning is as indicated on page 5 of the specification. While the specifications may define some exact amino acid substitutions, these substitutions are not controlling for the broad generic claim. The claims drawn to "null IGF" are drawn to "IGF-I which has amino acid sequence alterations at one or more sites in the molecule."

Appellants state that they have defined numerous null IGF with positions substations at positions 49, 50, 51, 53, 55 and 56. The activity is solely based on structures that have altered receptor binding activity. One cannot predict if a given modification in a peptide will have desired results in the inhibition of tumor growth. As stated previously, "'Direct' approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task. '(see page 492 in Ngo et al.) Accordingly, it is not know if an efficient algorithm for predicting the structure exist for a protein or peptide from it amino acid alone (see page 492 in Ngo et al.). Although the reference does not entirely rule out the algorithm, Ngo states that too many variables exist in obtaining an efficient

algorithm. For example, the "Not knowing the computational complexity of side chain structure predication leaves the algorithm developer in the quandary of not known whether inexact methods are truly necessary..." (see page 495). Therefore, clearly one could not predict the three dimensional structure based on structure of peptide alone. If one cannot predict the three dimensional structure, one cannot readily ascertain if the amino acid modification will allow the protein to conform to the necessary structure to recognize the desired receptor, in this case IGFBP-3. The true fact of the state of the art in peptide chemistry is expressed succinctly in the Rudinger article (see the conclusions in particular). "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study." Accordingly, one would be burdened with undue experimentation to determine which of the amino acids substitutions in the Null IGF will result in the desired activity. Note that Bayne et al. (*J. Of Biol. Chemistry,* Vo. 265, No. 26) teach that replacement of Tyr 24 and/or Tyr 31 in IGF-1 affected the binding activity of the peptide to the IGF-1 receptor. However, the reference further states that it could not be concluded "from our data whether the changes in affinity upon replacement of residues Tyr24 and/or Tyr31 are due to side chain or main chain interactions with the type 1 IGF receptor." (See page 15651). This implies, again, that one of ordinary skill cannot predict if the activity based on structure alone.

Appellants rely upon the single example of Y60L to argue that one of skill in the art would expect that replacing the 60th amino acid would disrupt IGF receptor binding and in turn be able to treat tumors as claimed. It is asserted that the Enablement prong of the 35 U.S.C. 112 does not require that every embodiment be exemplified. While it is correct that the MPEP states "[a]s long as the specification discloses at least one method of making and use the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35

U.S.C. 112 is satisfied," the instant application has not provided ample guidance for one to conclude that the single example of Y60L "bears a reasonable correlation to the entire scope of the claim." A single point mutation in a protein cannot be reasonable basis to conclude that any mutation, in any degree and in any location will achieve the same results as Y60L. As Rudinger concludes "[t]he significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study." Thus, an assumption of altering the 60th amino acid in the IGF molecule will result in the same activity as Y60L cannot be reasonably concluded. Appellants state that the art recognizes the replacement of the 60th amino acid in the IGF molecule results in the disruption of IGF receptor binding. However, for the desired activity to be achieve, i.e. treatment of tumors, not only must there be "a lower affinity for an IGF-I receptor but are still able to bind the major IGFBP-3 binding protein at least as well as wild-type IGF-I." There has been no evidence submitted by appellant, to date, that demonstrates that substitution of the 60th amino acid or any other amino acid in the 70 amino acid chain, to any degree, will not only decrease the IGF-1 receptor affinity but still maintain the ability to bind IGFBP-3 binding protein. Appellants are reminded that claims 1 and 16 of the instant application are open to any "null IGF."

Appellants argue that the enablement requirement does not require a per se rule that an animal model, used to support the claim of biological activity, be "art recognized." "Unless there is specific reason to doubt the correlation between a certain experimental animal and treatment of the disease condition itself, the evidence should be accepted presumptively." The art cited states clonogenic assays are not always helpful since they "can't always predict how a tumor will respond to a drug in an animal" and "[s]ometimes they don't work because the cells simply fail to divide n culture." (See Gura, page 1042). Xenograft models in mice "don't behave like naturally occurring

tumors in humans--they don't spread to other tissues." (See Gura, page 1041). The Jain article states that for solid tumors, the clinical results to date have not met the high expectation obtained as a result of in in-vitro testing (see the paragraph of page 1079-1080). "Even with the best animal model, however, we still need to better understand how the process of biodistribution of various agents 'scales-up' from mouse to human. The biochemical and physiological differences between these species make this knowledge critical." Thus, unlike Appellants arguments, there is reason to doubt the correlation animal models for cancer and the treatment of the disease in human. The references cited by Applicants do not indicate nor conclude that PC-3 models behave like naturally occurring prostate tumors in human and are predictive of how the tumor will respond to a drug. The MPEP states that the standard for determining an enabling disclosure is reasonableness. See MPEP 2164.04. The references cited in the previous office action provide sufficient "reasonable basis to question the enablement" for the treatment of cancer and the decrease in growth of a tumor. The mere fact none of the references indicate that there is no association between the pathogenesis of cancer in an animal model and a human is inconsequential since the references disclose the unpredictability associated with the human and animal model association.

Here, the correlation to humans is even more difficult since the claims are drawn to any tumor and any cancer. It is know in the art that the PC-3 model relied upon by Appellants is a prostate cancer model. Appellants have not provided any other models that would correlate to the other types of cancer claimed. If the art indicates the unpredictability associated with a PC-3 model to prostate cancer, it would be even more unpredictable to correlate the activity form the PC-3 model to other types of cancer. Lung and breast cancers are known to be solid tumors. The Jain article states that for solid tumors, the clinical results to date have not met the high expectation obtained as a result of in in-vitro testing (see the paragraph of page 1079-1080). "Even with the

best animal model, however, we still need to better understand how the process of biodistribution of various agents 'scales-up' from mouse to human. The biochemical and physiological differences between these species make this knowledge critical."

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

ANISH GUPTA
PRIMARY EXAMINER

Anish Gupta
July 25, 2005

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